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Hemorrheological changes associated with brain death and their implications for potential organ donors

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Abstract Successful transplantation of donor organs from brain-dead patients requires adequate maintenance of hemodynamic parameters. Blood flow and tissue perfusion are highly dependent upon hemorrheology. The aim of the present study was to evaluate hemorrheological parameters in potential organ donors compared to healthy volunteers. Whole blood-, plasma- and corrected blood viscosity, hematocrit, erythrocyte deformability, and erythrocyte aggregation were obtained in ten consecutive brain-dead patients and ten matched volunteers. Compared to controls, hematocrit and whole blood viscosity at high and medium shear rates and erythrocyte deformability were significantly decreased. Plasma viscosity was significantly increased in all patients. In the same group, a highly significant increase was observed at all shear rates when viscosity was corrected for hematocrit. Definite rheological abnormalities were found in the blood of brain-dead patients, something which might lead to impaired organ function after transplantation. Therefore, optimizing such parameters by special fluid management may be of importance in potential organ donors.

Key words Brain death, hemorrheology · Hemorrheology, brain death · Blood viscosity, organ donors · Donors, brain-dead, blood viscosity

Introduction

Successful transplantation of donor organs can offer patients with end-stage organ failure a better prognosis. However, the demand for donor organs is increasing each year and already exceeds the available supply. Therefore, optimal management of potential organ donors and, in particular, maintenance of optimal tissue perfusion are of great importance [1, 16, 19].

In most cases, organs for transplantation are procured from brain-dead donors. For successful donation of perfusable organs, continued maintenance of cardiovascular function and use of artificial respiration are required until the organs can be removed. Hypotension resulting from altered cardiovascular control mechanisms and hypovolemia are common after brain death [1, 4, 12, 16, 18, 19] and will result in poor tissue perfusion if not adequately treated. Hypovolemia is mostly caused by the neurogenic diabetes insipidus commonly observed in brain-dead patients. Appropriate fluid management is, thus, one of the cornerstones of donor maintenance [19]. Blood flow and, hence, tissue perfusion are

Table 1 Individual data from all brain-dead patients

No.	M/F	Age	Underlying cause	Organ donor
1	M	41	Cerebral contusion (traffic accident)	no
2	F	57	Subarachnoidal hemorrhage	yes
3	M	38	Subarachnoidal hemorrhage	no
4	F	56	Subarachnoidal hemorrhage	yes
5	F	49	Intracerebral hemorrhage	yes
6	F	48	Subarachnoidal hemorrhage	yes
7	M	44	Subarachnoidal hemorrhage	yes
8	F	22	Cerebral contusion (traffic accident)	yes
9	M	29	Subarachnoidal hemorrhage	no
10	M	16	Cerebral contusion (traffic accident)	yes

highly dependent upon blood viscosity, which in turn is determined by hematocrit (Hct), plasma viscosity, erythrocyte aggregation, and erythrocyte deformability. These parameters may therefore play an important role in donor management.

Hemorrheology deals with the flow and deformation behavior of blood [14]. When pressure is applied to a fluid, layers of molecules slide over each other and the fluid is said to be sheared. The velocity gradient between the two layers, which move with different velocities, is called the shear rate. Shear stress is the force that is required to cause the layers to slide over each other. Viscosity represents the ratio of shear stress to shear rate. The more viscous a material, the greater the shear stress required to cause it to flow at a particular speed. Shear rate is inversely proportional to the vessel radius. Due to the presence of corpuscular elements and their tendency to aggregate, blood viscosity, unlike plasma viscosity, varies with shear rate.

To our knowledge, hemorrheology has thus far not been investigated in brain-dead patients. The aim of this study was, therefore, to study hemorrheological parameters in potential organ donors.

Materials and methods

After the institutional ethics committee had approved the study, informed consent was obtained from the relatives of all ten consecutive brain-dead patients (aged 38 ± 11 years) for participation in this study, which was performed in accordance with the ethical standards laid down in the declaration of Helsinki. All patients met the criteria for brain death used in our hospital. These criteria are based on clinical findings and electroencephalographic examination. All patients (five male, five female) were potential organ donors. No extracerebral injuries were present. Demographic data are given in Table 1. Ten healthy volunteers (five male, five female), aged 35 ± 12 years, served as controls. Fluid management was performed using glucose 5 % solution (containing 30 mmol/l potassium chloride) and sodium chloride 0.9 % solution as crystalloid solutions and succinylated gelatin fluid (Gelofusine) as a colloidal solution. Fluid management, transfusion requirement, blood loss, and urine output were quantitated in all patients. Fluid management was aimed at maintaining a normal fluid balance. Blood pressure was maintained by means of the cardiotropic agent dopamine.

Blood samples from all patients and volunteers were drawn into 10-ml vacutainers containing dry disodium-ethylenediaminetetra-acetic acid for measurement of hemorrheological parameters. In the volunteers, blood samples were obtained after an overnight fast.

Blood and plasma viscosity were measured in a Contraves LS30 rotational viscometer (Contraves, Basel, Switzerland) at 37 °C. Blood viscosity was measured at 81 different shear rates ranging from 100 to 0.01 sec^{-1}. From this range three shear rates were selected, one representing a low shear rate (LS) at 0.05 sec^{-1}, one a medium shear rate (MS) at 0.5 sec^{-1}, and one a high shear rate (HS) at 70 sec^{-1}. Because plasma behaves as a newtonian fluid and plasma viscosity does not vary with shear rate, measurement was performed only at 70 sec^{-1}. Erythrocyte aggregation factor was derived from the ratio of whole blood viscosities measured at low and high shear rates [11]. Hematocrit was determined using a capillary tube microcentrifuge. In accordance with the guidelines issued by the International Committee for Standardization in Hematology, blood viscosity was also corrected to a standard hematocrit of 0.45 L/L [11]. Blood viscosity must be corrected for hematocrit in order to compare changes after eliminating this determinant. The correction was made using regression equations derived from 1500 subjects. Since blood with a relatively high Hct and low viscosity is capable of transporting more oxygen, the oxygen transport capacity was calculated at each shear rate as follows: Hct/HS viscosity, Hct/MS viscosity and Hct/LS viscosity [3].

Erythrocyte deformability was measured using a laser diffractometric method, also known as ektacytometry, which measures the elongation of erythrocytes under increasing shear stress (Laser-assisted Optical Rotational Cell Analyzer, Megatronics, Hoorn, The Netherlands). The erythrocyte elongation index (EI), which expresses erythrocyte deformability, was computed at the following shear stresses: 0.95 Pa ($EI_{0.95}$), 3 Pa (EI_3), 9.49 PA ($EI_{9.49}$), and 30 Pa (EI_{30}) [10]. Finally, the Taylor factor, an empirically derived factor thought to reflect erythrocyte deformability [5, 7, 9], was calculated as follows: T = 1 – (plasma viscosity/HS viscosity)$^{0.4}$/Hct.

All measurements were made in duplicate within 2 h after blood sampling. All data are expressed as means ± SD. Statistical analysis was performed using the Mann-Whitney test to evaluate statistically significant intergroup differences. The null hypothesis was rejected if P was below 0.05.

Results

In one patient two units of packed cells were transfused 40 h prior to the development of an isoelectric electroencephalograph. The final fluid balance in the 12 h prior to declaration of brain death was either balanced or negative in all patients (Table 2). Insensible fluid loss was not included in the fluid balance. No major blood loss was observed. The mean dosage of dopamine in the 12 h preceding declaration of brain death was 7 ± 4 µg/kg per min. In all cases blood was sampled within 30 min after declaration of brain death.

Compared to healthy volunteers, Hct and blood viscosity at high and medium shear rates were significantly decreased in all patients. No significant difference was observed in low shear viscosity and erythrocyte aggrega-

Table 2 Fluid management (in ml) in the 12 h prior to declaration of brain death (insensible fluid loss is not included)

	Mean ± SD
Total crystalloid solutions	2952 ± 2298
Total colloid solution	2214 ± 1030
Diuresis	6379 ± 2942
Blood loss	0 ± 0

Table 3 Results in means ± SD (*corr. viscosity* viscosity corrected to Hct of 0.45)

	Brain-dead patients	Controls	*P*-value
Hct (L/L)	0.32 ± 0.04	0.43 ± 0.02	0.0001
Plasma viscosity (mPa.sec)	1.53 ± 0.17	1.33 ± 0.07	0.004
HS viscosity (mPa.sec)	4.30 ± 0.39	5.06 ± 0.53	0.0008
MS viscosity (mPa.sec)	17.0 ± 4.0	25.7 ± 5.8	0.002
LS viscosity (mPa.sec)	46.7 ± 19.4	60.8 ± 16.7	0.096
Aggregation factor	10.9 ± 4.6	11.9 ± 2.3	0.34
Corr. HS viscosity (mPa.sec)	6.86 ± 0.7	5.36 ± 0.3	0.0002
Corr. MS viscosity (mPa.sec)	47.7 ± 17.8	29.1 ± 4.3	0.0003
Corr. LS viscosity (mPa.sec)	215.5 ± 182.5	71.9 ± 12.6	0.0005
$EI_{0.95}$	0.152 ± 0.059	0.194 ± 0.036	0.072
EI_3	0.353 ± 0.021	0.372 ± 0.025	0.13
$EI_{9.49}$	0.494 ± 0.011	0.516 ± 0.016	0.007
EI_{30}	0.568 ± 0.016	0.590 ± 0.008	0.0009

tion factor. Plasma viscosity was significantly increased in patients compared to controls. A highly significant increase in corrected viscosity was observed at all shear rates.

The erythrocyte elongation index was significantly decreased at the higher shear stresses ($EI_{9.49}$ and EI_{30}). A decrease in deformability was also observed when the elongation index was measured at 0.95 and 3 Pa ($EI_{0.95}$ and EI_3); however, these decreases did not reach significance. The Taylor factor was found to be significantly increased compared to controls (1.07 ± 0.08 vs 0.95 ± 0.01, $P = 0.0002$), indicating reduced deformability. The above results are presented in Table 3.

Finally, the calculated oxygen transport capacity was found to be significantly decreased at the high shear rate (Hct/HS; $P = 0.0009$). At medium and low shear rates (Hct/MS and Hct/LS) no significant differences were observed.

Permission for organ transplantation was obtained in seven cases.

Discussion

In the present study our aim was to investigate hemorrheological parameters in patients who had been declared brain-dead. The results show that many rheological parameters were reduced (Hct, high and medium shear viscosity, and erythrocyte deformability) while others were increased (plasma viscosity and corrected viscosity at all shear rates) in these patients.

In the microvasculature, optimal tissue perfusion is dependent upon the rheology of blood. Erythrocyte deformability plays an important role since the diameter of a capillary is about half that of an erythrocyte. Therefore, an erythrocyte must be capable of deforming to traverse the microvasculature and, hence, to deliver oxygen to the tissues. In this study, a decrease in erythrocyte deformability, measured as EI, was found that was statistically significant at higher shear stresses. As the microvasculature is a region with a high shear rate, these findings may explain the reduced calculated oxygen transport capacity at high shear rates in these patients.

Additionally, the Taylor factor, an empirically derived calculated factor thought to reflect erythrocyte deformability, was significantly increased. An increased Taylor factor is thought to indicate decreased deformability. However, in a previous study in patients undergoing coronary artery surgery, no correlation was established between the Taylor factor and EI [15]. Thus far, there is no consensus as to the clinical meaning of this factor. Dintenfass et al. [6] found in a heterogenous group of severely ill medical patients that the Taylor factor correlated with the severity of their illness. It was hypothesized that the Taylor factor could be used as an indicator of the patient's clinical status. In our study, the increased Taylor factor could be explained by the decrease in EI and/or the severity of illness, as these patients actually died.

In these same patients, a highly significant reduction in Hct was demonstrated, accompanied by a statistically significant decrease in whole blood viscosity at high and medium shear rates. Since aggressive fluid resuscitation is often used to maintain normal blood pressure, the reduction in Hct is often thought to be the result of dilution. However, as mentioned above, none of the patients had a positive fluid balance and no major blood loss had occurred. It should be noted that this calculation is not a measurement of intravascular volume. In a different patient group, however, in which aggressive fluid management was also required, similar Hct reductions and concurrent changes in blood viscosity were not observed [15]. In the present study, age and sex-matched healthy individuals were used as a control group since all patients were ASA I class patients prior to the event leading to brain death.

Erythrocyte deformability is a major determinant of red cell survival. During passage through the spleen,

the red blood cells must traverse extremely narrow endothelial slits with a diameter of approximately 1 μm. A reduction in deformability may impair passage of these cells, resulting in splenic sequestration and destruction [13, 14]. Whether this mechanism can explain the decreased Hct in brain-dead patients remains to be elucidated.

The significant increase in plasma viscosity could be responsible for the observation of unaltered low shear whole blood viscosity and erythrocyte aggregation factor. The viscosity of plasma is mainly determined by the concentration of protein components, the most important of which is fibrinogen, known as an acute phase protein. Furthermore, these proteins enhance erythrocyte aggregation, often resulting in a relative increase in low shear viscosity [14].

When alterations in Hct were eliminated by correcting viscosity to a standard Hct of 0.45, viscosity in patients was found to be very significantly elevated compared to that in controls. It is unlikely that the observed decreased erythrocyte deformability, which plays an important role in high shear viscosity, and the increased plasma viscosity were responsible for the increased corrected blood viscosity observed at all shear rates. In a previous study in patients undergoing cardiopulmonary bypass surgery, it was hypothesized that an additional factor might play a role in determining whole blood viscosity [15], one based on the fact that viscosity, when corrected for its most important determinant, hematocrit, still showed an increase compared to baseline values. This observation was made while all other determinants had returned to baseline. Dintenfass has suggested that an autoregulatory control mechanism exists for the rheology of blood that detects changes by means of two different viscoreceptors; α-viscoreceptors, which detect changes in whole blood viscosity, and β-viscoreceptors, which detect rigidity of the red blood cells. It was hypothesized that these receptors are located in certain arterioles and capillaries [8], possibly in the vessels of the brain. This hypothesis may explain the rheological abnormalities found in the patients in the present study.

Based on the abnormalities in hemorrheological parameters observed in this study, it may be worth investigating whether a special regimen of intravenous fluids would optimize organ preservation in potential organ donors. As for the type of fluids, a combination of colloids and crystalloids, depending on fluid depletion and electrolyte status, respectively, should be adequate [2, 17]. Colloidal solutions should be chosen with regard to their specific rheological properties. At present, we are performing an investigation into the hemorrheological properties of the different colloidal solutions currently available (gelatines, hydroxyethyl starches, and dextran solutions). A hematocrit of 0.25–0.30 L/L should probably be maintained to optimize hemorrheology and organ perfusion.

Even though it seems that the rheologic abnormalities we measured are caused by brain death itself and not by the concurrent fluid therapy, this cannot be concluded on the basis of these results alone. Therefore, we are presently working on a follow-up study in patients with severe head injuries in which hemorrheologic parameters are measured starting immediately after admission to the hospital in order to evaluate the time course of the changes described above. It will then be possible to compare differences in parameters between the patients with head injuries and those who eventually become brain-dead. Additional parameters that may be of importance in such patients such as hemodynamics, and endocrinological measurements will also be investigated. It should be kept in mind that although the exact cause of the abnormalities described is not certain, they are present in these patients at the time of donation. To evaluate a possible role of the rheologic changes in impaired organ function after transplantation, transplantation studies are needed that compare groups with different rheological properties.

In conclusion, this study demonstrates that even though the main component of blood viscosity – hematocrit – is decreased in all brain-dead patients, corrected blood viscosity is increased in these patients. In addition, erythrocyte deformability is decreased compared to that in healthy volunteers. These findings may be of importance in the management of potential organ donors.

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